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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,445	07/26/2006	Tadaaki Ohgi	20855/0205063-US0	1266

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EXAMINER	
GOON, SCARLETT Y	

ART UNIT	PAPER NUMBER
4131	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,445	OHGI ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	4131	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *11-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-22* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :26 July 2006 and 11 February 2008.

DETAILED ACTION

This application is a National Stage entry of PCT/JP05/00974 filed on 26 January 2005 and claims priority to foreign application Japan 2004-018060 filed on 27 January 2004. A certified copy of the foreign priority document in Japanese is received.

Information Disclosure Statement

The information disclosure statement (IDS) dated 26 July 2006 and 11 February 2008 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Election/Restrictions

Applicants' election with traverse of Group II, encompassing claims 4-10 and 18-22, drawn to the method for producing the ribonucleic acid in said claims, in the reply filed on 7 March 2008, is acknowledged.

The traversal on the grounds that the claims in Group I encompasses the same ribonucleic acid, represented by general formula (1) as Group II, and therefore is not a serious search burden, was considered and found persuasive. Accordingly, Groups I and II, encompassing claims 1-10 and 18-22, will be examined on its merits herein as one group.

Claims 11-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and nonelected species, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by den Hartog *et al.*

Applicants claim a ribonucleic acid compound represented by general formula (1). Applicants further claim the ribonucleic acid compound of claim 1, wherein R^{20} is H, 2-cyanoethyl, or 2,2,2-trichloroethyl, and R^{21} is 2-chlorophenyl or 2-chloro-4-tert-butylphenyl.

den Hartog *et al.* teaches the chemical synthesis of a messenger ribonucleic acid fragment. The synthesis of the octadecaribonucleotide begins with the preparation of properly protected mononucleotides (p. 1012, Scheme I and under "Results and Discussion" heading). According to Scheme 1, the 5'-OH position of ribonucleotide (1), protected at the 2'-OH position with a 4-methoxytetrahydropyranyl group, can be regioselectively levulinylated by levulinic acid in the presence of DCC. The resulting compound (5) can then be phosphorylated at the 3'-OH position with the monofunctional

reagent 2,2,2-tricholoroethyl 2-chlorophenyl phosphorochloridate to yield compound (6). The 4-methoxytetrahydropyranyl group at the 2-OH position can be selectively removed under acidic conditions (pH 2) at 20 °C for 2 hours (p. 1015, second column, last paragraph; scheme VI – conversion of compound 18b to 19).

Compound (6) of Scheme 1 (p. 1012), disclosed by den Hartog *et al.*, anticipates instant claims 1 and 3.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Section [0001]

Claims 4-6, 8, 19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over den Hartog *et al.* as applied to claims 1 and 3 above, and further in view of García *et al.*

Applicants claim a method for producing ribonucleic acid compound (3), by levulinylating compound (2) with a lipase and a levulinylating agent. Compound (3) can then be phosphorylated to yield compounds (1a) or (1b). The applicants further claim the levulinylating agent is levulinic acid, levulinic anhydride, a levulinate ester or a levulinoyl halide.

The teachings of den Hartog *et al.* are as described above in the claim rejections under 35 USC § 102. den Hartog *et al.* does not teach a method wherein a lipase directs the levulinylating reaction. This deficiency is addressed by García *et al.*

García *et al.* teaches a method for the enzymatic synthesis of levulinyl protected nucleosides that are useful for solution phase synthesis of oligonucleotides. As shown in Scheme 2 (p. 3535), regioselective acylation of the 5'-OH of compound (5) can be achieved with acetonoxime levulinate in the presence of lipase CAL-B. The starting

material used in the reactions is 2'-deoxy ribonucleotides. The levulinyl protected nucleosides can be used in the synthesis of oligo-deoxynucleosides.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of den Hartog *et al.*, concerning the chemical synthesis of a ribonucleotide fragment by combining properly protected mononucleotides, with the teachings of García *et al.*, regarding the enzymatic synthesis of levulinyl protected nucleosides. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by García *et al.*, that preparation of nucleotide building blocks involves tedious chemical protection/deprotection steps which can be avoided by using enzymatic methods.

In-so-far as the den Hartog *et al.* and García *et al.* references do not teach the use of levulinic acid, levulinic anhydride, a levulinate ester or a levulinoyl halide as the levulinylating agent, the CAL-B enzyme used by García *et al.* in levulinylating the ribonucleotide is the same as that recited in the instant application. Therefore, the reaction employing the lipase and the levulinylating agent, as described in the instant claims or the reference, would necessarily produce the same result. A skilled artisan would be able to choose the levulinylating agent that is most accessible and also most suitable to their methods.

Absent of any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in using the enzymatic method described by García *et al.* to levulinylate the 5'-OH group of the

ribonucleotide starting material described by den Hartog *et al.*, and then use the resulting levulinylated compound to synthesize the phosphorylated ribonucleotide.

Section [0002]

Claims 2, 7, 18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over den Hartog *et al.* and García *et al.* as applied to claims 1, 3-6, 8, 19 and 21 above, and further in view of Iwai *et al.* and Greene *et al.*

Applicants claim a ribonucleic acid compound and a method for the synthesis of such compound as described above for claim rejections under 35 USC § 102 and section [0001] of 35 USC § 103. Applicants further claim the method and compound wherein R^1 is a 2-tetrahydrofuranyl or 1,3-dioxolan-2-yl group.

The teachings of den Hartog *et al.* and García *et al.* are as described above in the claim rejections under section [0001] of 35 USC § 103. The 2'-OH of the ribosyl compound described by den Hartog *et al.* is protected with a 4-methoxytetrahydropyranyl group. den Hartog *et al.* does not teach the compound and method wherein the 2'-OH position is protected with a 2-tetrahydrofuranyl or 1,3-dioxolan-2-yl group. This deficiency is addressed by Iwai *et al.* and Greene *et al.*

Iwai *et al.* teaches the synthesis of oligonucleotides by solid-phase techniques. The mononucleotide units that Iwai *et al.* used to synthesize the oligonucleotides consist of 2'-tetrahydrofuranyl ribose derivatives (p. 3762, Fig. 1 formula (5)).

Greene *et al.* teaches that both a 2-tetrahydrofuranyl protecting group and a 4-methoxytetrahydropyranyl protecting group can be removed under similar mild acidic

conditions (p. 34 number 21; p. 35 number 26; p. 413-414, Reactivity Chart 1, PG 12 and 15).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of den Hartog *et al.*, concerning the chemical synthesis of a ribonucleotide fragment by combining properly protected mononucleotides, with the teachings of García *et al.*, regarding the enzymatic synthesis of levulinyl protected nucleosides, with the teachings of Iwai *et al.*, regarding the synthesis of oligonucleotides from mononucleotide units containing a 2'-tetrahydrofuranyl group on ribose, with the teachings of Greene *et al.*, regarding the similar conditions used to deprotect a 2-tetrahydrofuranyl and a 4-methoxytetrahydropyranyl group. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Greene *et al.*, that the protecting groups have similar properties and are removed using similar conditions, thereby providing a skilled artisan with multiple alternatives to use in protecting a 2'-OH group based on the reagents available.

Absent of any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in using a 2'-tetrahydrofuanyl protected ribose derivative as described by Iwai *et al.* to synthesize the phosphorylated nucleotide described by den Hartog *et al.*

Section [0003]

Claims 9, 10 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over den Hartog *et al.* and García *et al.*, as applied to claims 1, 3-6, 8, 19 and 21 above, and further in view of Broka *et al.*

Applicants claim a ribonucleic acid compound and a method for the synthesis of such compound as described above for claim rejections under 35 USC § 102 and section [0001] of 35 USC § 103. Applicants further claim the method wherein the phosphorylating agent is 2-chlorophenyl phosphoroditriazolide, 2-chlorophenyl-O,O-bis(1-benzotriazolyl)phosphate or 2-chloro-4-tert-butylphenyl phosphoroditriazolide, and the reagent for protecting a phosphate group is 3-hydroxypropionitril or 2,2,2-trichloroethanol.

The teachings of den Hartog *et al.* and García *et al.* are as described above in the claim rejections under 35 USC § 102 and section [0001] of 35 USC § 103. den Hartog *et al.* and García *et al.* do not teach a method wherein the phosphorylating agent is 2-chlorophenyl phosphoroditriazolide, 2-chlorophenyl-O,O-bis(1-benzotriazolyl)phosphate or 2-chloro-4-tert-butylphenyl phosphoroditriazolide, and the reagent for protecting a phosphate group is 3-hydroxypropionitril or 2,2,2-trichloroethanol. This deficiency is addressed by Broka *et al.*

Broka *et al.* teaches a simplified method in the synthesis of short oligonucleotide blocks. As shown in Figure 1 (p. 5463), nucleoside (III) can be phosphorylated with O-chlorophenylphosphoroditriazolide (II) to yield the monotriazolide (IV) (p. 5462, subheading "Results and Discussion"). Monotriazolide (IV) can then be hydrolyzed to give the charged phosphate (V). Alternatively, the monotriazolide (IV) can be treated

with 3-hydroxypropionitrile to protect the phosphate group with a cyano-ethyl group to provide fully protected mononucleotide (VII) (p. 5464). Yet another alternative is that monotriazolide (IV) can be coupled with the 5-OH group of another nucleotide (VI) to yield dinucleotide (VIII).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of den Hartog *et al.*, concerning the chemical synthesis of a ribonucleotide fragment by combining properly protected mononucleotides, with the teachings of García *et al.*, regarding the enzymatic synthesis of levulinyl protected nucleosides, with the teachings of Broka *et al.*, regarding a simplified method in the synthesis of short oligonucleotide blocks. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Broka *et al.*, that their method is more efficient and simple compared to using bifunctional phosphorylating reagents which typically results in undesired dimer products (p. 5462).

Absent of any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in using the phosphorylating scheme as setforth by Broka *et al.* to phorsphorylate the ribonucleotide compounds described by den Hartog *et al.*

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Cecilia Tsang can be reached on 571-272-0562 or Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JANET L ANDRES/
Supervisory Patent Examiner, Art Unit 4131

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